Review

Pathogen Genomics and Host Cellular Susceptibility Factors of COVID-19

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ABSTRACT

Coronavirus disease 19 (COVID-19) caused by infection with a novel severe acute respiratory syndrome virus -2 (SARS-CoV2) has evolved into a pandemic and a global public health emergency. The viral genomics, host cellular factors, and interactions are critical for establishing a viral infection and developing a related disease. This paper aims to provide an overview of viral genomics and discuss host cellular factors so far identified to be involved with the disease susceptibility. The novel pathogen is a beta coronavirus and one of seven that cause diseases in humans. It is a single strand positive-sense RNA genome virus that encodes 27 proteins, including the structural Spike protein that binds to host cell surface receptors and is a key for viral entry, and 16 nonstructural proteins that play a critical role in viral replication and virulence. While the angiotensin-converting enzyme, ACE2 receptor, and the proteases TMPRSS2 and furin are established as necessary for viral entry, host factors CD147, Cathepsins, DPP4, GRP78, L-SIGN, DC-SIGN, Sialic acid, and Plasmin(ogen) may also play a role in the viral entry. The Spike protein and nonstructural proteins, and various host factors working together may contribute to the infection kinetics, high infectivity, rapid transmission, and a spectrum of clinical manifestations of COVID-19. More importantly, they can serve as potential targets in developing strategies for therapeutical prevention and intervention.

KEYWORDS

SARS-CoV-2, genomics and genetics, viral-host interaction, susceptibility, COVID-19

INTRODUCTION

Coronavirus infectious disease 2019 (COVID-19) is a new respiratory disease with a rapid transmission and high infectivity. Some individuals who become infected may develop acute respiratory disease syndrome (ARDS) and a cytokine storm (1, 2), the sequelae of which can be life-threatening. The pathogen is defined and classified through the whole genome-sequencing as the second severe acute respiratory syndrome coronavirus (SARS-CoV-2) and is 80% identical to severe acute respiratory syndrome virus (SARS-CoV). SARS-CoV-2 has a high sequence similarity (96%) with a bat coronavirus, but its natural host remains uncertain (3, 4). SARS-CoV was more lethal and has not been reported to cause additional infections in nearly two decades, while SARS-CoV-2 has a rapid human-to-human transmission mode that enabled it within a short period to cause the ongoing pandemic and global public health emergency. SARS-CoV-2 and COVID-19 will be of great challenge to human medicine and public health in years to come, requiring a significant amount of time and effort to research and develop appropriate prevention and therapeutic measures.

SARS-CoV-2 is the sole etiological factor for COVID-19, but the risk of developing the disease and clinical manifestations are affected by pathogen-host interaction. Exogenous factors or activities associated with a higher likelihood of exposure to the pathogen and endogenous host factors modulating the viral entry into the host cells may sequentially contribute to the disease risk and finally

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determine the status of infection and its severity COVID-19. Understanding the pathogen's genomic and genetic factors, viral replication cycle, and human host factors may help to develop vaccines and drugs to prevent and treat individuals with COVID-19. This article aims to describe the genomics and genetics of SARS-CoV-2, its replication, and host cellular factors necessary for the viral entry into the host cell to cause the infection and further develop the disease. It will not consider host factors that may influence the sequelae of the infection and clinical outcomes.

CORONAVIRUS AND HUMAN DISEASES

Classification of coronavirus

Coronaviruses (CoV) are enveloped viruses with a single strand and positive-sense RNA genome that can infect mammals and birds. They are classified into three groups based on genetic and serological evidence. Group I includes human coronavirus (HCoV) 229E and NL63, transmissible gastroenteritis virus of swine (TGEV), and porcine epidemic diarrhea virus (PEDV). Group II includes murine hepatitis virus (MHV), bovine coronavirus (BCoV), HCoV OC43, SARS-CoV, the Middle East respiratory syndrome (MERS-CoV), porcine hemagglutinating encephalitis virus (PHEV), rat sialodacryoadenitis virus (5), canine coronavirus, and equine coronavirus (6). Group III includes avian infectious bronchitis virus (IBV). These coronaviruses have been shown to cause respiratory, enteric, hepatic, and neurological diseases in humans and animals. Even domestic animals are arguably susceptible to SARS-CoV-2 (7, 8).

Coronaviruses are currently grouped into four genera with gene sources in bats and avian species (**Table 1**). According to the International Committee on Taxonomy of Virus (ICTV), the coronaviruses belong to the family *coronaviridae* under the order *nidovirales*. They are *alphacoronavirus*, *betacoronavirus, gammacoronavirus*, and *delta coronavirus* genera (9). Animal surveillance indicates that bat coronaviruses mainly have gene sources of *alphacoronavirus* and *betacoronavirus*, accounting for most coronaviruses (10). In contrast, avian coronaviruses are gene sources of *gammacoronavirus* and *deltacoronavirus* (11). The coronaviruses can infect different animal species and replicate in the plasma of host cells after infection.

Table 1. Classification of coronavirus

Genus	Abbreviation	Full name	Human CoV
Alpha	FIPV	Feline Infectious peritonitis virus	
	PRCV	Porcine respiratory coronavirus	
	TGEV	Transmissible gastroenteritis virus of swine	
	Rh-BatCoV HKU2	Rhinolophus bat coronavirus HKU2	
	SDAS-CoV	Swine acute diarrhea syndrome coronavirus	
	HCoV-NL63	Human coronavirus NL63	Human
	HCoV-229E	Human coronavirus 229E	Human
	Mi-Bat-CoV 1A	Minopterus bat coronavirus 1A	
	Mi-BatCov HKU8	Minopterus bat coronavirus HKU8	
	Sc-BatCoV 512	Scotophilus bat coronavirus 512	
	PEDV	Porcine epidemic diarrhea virus	
Beta	HCoV-OC43	Human coronavirus OC43	Human
	ECoV	Equine coronavirus	
	PHEV	Porcine hemagglutinating encephalomyelitis virus	
	CRCOV	Canine respiratory coronavirus	
	BCoV	Bovine coronavirus	
	MHV	Murine herpesvirus	
	HCoV-HKU1	Human coronavirus HKU1	Human
	SARS-CoV	Severe acute respiratory syndrome coronavirus	Human
	SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2	Human
	MERS-CoV	The Middle East respiratory syndrome coronavirus	Human
	btCoV-HKU4	Bat coronavirus HKU4	
	btCoV-HKU5	Bat coronavirus HKU5	
	btCoV-HKU9	Bat coronavirus HKU9	
Gamma	BWCOV SW1	Beluga whale coronavirus SW1	
	TCoV	The turkey coronavirus	
	IBV	Avian Infectious bronchitis virus	
Delta	Bu-CoV-HKU11	Bubaline coronavirus	
	MunCoV HKU13	Munia coronavirus	
	ThCoV HKU12	Thrush coronavirus	

Human coronaviruses and diseases

Human coronavirus (HCoV) is a coronavirus that can cause disease in humans and has a person-to-person transmission mode. So far, there have been seven HCoVs identified (**Table 1**). Of the seven HCoVs, OC43, 229E, NL63, and HKU1 often cause mild diseases, including the common cold. They are called non-severe acute respiratory syndrome (SARS)-like coronavirus. The other three coronaviruses are novel zoonotic, are highly pathogenic, and can cause severe infectious diseases in humans.

The first two HCoVs (OC43 and 229E) were isolated and caused common cold and minor upper respiratory infections in the 1960s (12, 13). Seroepidemiologic studies detected outbreaks of disease with a 229E-like virus and other coronaviruses such as OC38 and OC43 (14, 15). OC43 and related strains may account for a considerable proportion of common cold or respiratory tract infection (14). The outbreak of a severe viral respiratory disease in 2002 led to the identification of SARS-CoV (16). The infection with SARS-CoV can cause humans to develop flu-like symptoms and pneumonia after an incubation period of 4-6 days. A total of 8098 people were diagnosed with SARS-CoV infection, 774 people died, yielding a case fatality of 8.7%.

Since the SARS outbreak, several new HCoVs have been identified. In 2004, HCoV-NL63 was isolated from a 7-month-old child with bronchitis (17), and it was identified later as a causative agent for a lower respiratory tract disease (18). A year later, HCoV-HKU1 was isolated in nasopharyngeal biospecimens and identified as a causative agent for an indexed patient with pneumonia in Hong Kong (19). In 2012, the Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV) was identified as a novel corona-virus causing SARS-like respiratory disease in Saudi Arabia (20), leading to the first outbreak of MERS with more than 2080 laboratory-confirmed cases and 722 related deaths, a fatality rate of 34.7%. In late 2019, the SARS-CoV-2 virus was isolated and reported from a few pneumonia patients in Wuhan, China (3).

The natural origin of HCoVs

All seven HCoVs have natural animal origins of either bat or rodents (10). Of the three HCoVs that can cause the acute severe respiratory syndrome, SARS-CoV was transmitted to humans by the civet cat, while MERS-CoV was by the dromedary camel, and SARS-CoV-2 was likely by pangolins. HCoVs are related in structure and replication to neuroinvasive animal coronaviruses, including porcine hemagglutinating encephalitis virus (PHEV), feline coronavirus (FCoV), and mouse hepatitis virus (MHV). All can invade the central nervous system and cause neuropathology (21). HCoV 229E can infect human lung fibroblasts, and the cellular receptor, human amino-peptidase N (APN, also known CD13) (22), a zinc-dependent metalloprotease, which is also a receptor for FCoV sero-type II, TGEV, PEDV, and the canine coronavirus that causes diseases to animals (23).

GENOMIC STRUCTURE AND GENETICS

The viral genomic structure

Coronaviruses are named for their large spike projections from the envelope, making the virus a crown-like shape (**Figure 1A**). It contains the nucleocapsid, consisting of the genome RNA packaged inside the helical capsid formed by the phosphorylated nucleocapsid (N) protein, enclosed with nonstructural proteins inside the envelope of a phospholipid lipid bilayer derived from the membrane of host cells (24). The envelope also consists of structural proteins, including spike (S) glycoprotein, hemagglutinin-esterase (HE), membrane (M) protein, and the enveloped (E) protein, plus the glycan groups and ORF7a accessory protein (24).

The genome of SARS-CoV-2 is about 29.9kb, comprising 14 open reading frames (ORFs) and encodes 27 proteins (**Figure 1B** and **1C**). It consists of a 5' untranslated region (5'UTR), a replicase (ORF1ab), S, E, M, N, a 3' untranslated region, and other open reading frames (ORFs) that have yet to be characterized (25) but which likely encode accessory proteins required for viral replication inside the host cells. The viral particles include 16 nonstructural proteins (nsp1-nsp16) that are required for viral repli-cation and modulate pathogenesis, four structural proteins (S, E, M, N) that are important for viral subtyping and response to vaccines, and other accessory proteins including 3a, 3b, 6, 7a, 7b, 8, 9b, 9c, and 10 (26, 27). While SARS-CoV-2 has a high similarity in genomic structure with two other beta-coronaviruses that cause SARS and MERS in humans, both diseases seem to be more severe in terms of case fatality. MERS, even more so than SARS. However, they lack the fast human-to-human transmission mode characteristic of COVID-19.

The replicase locus and proteins

Nonstructural proteins

The replicase locus of SARS-CoV-2 contains two substantial open reading frames (ORFs), ORF1a and ORF1b, which span about 20 kb and two-thirds of the genome. The ORF1a encodes a polyprotein (pp) 1a while ORF1a and ORF1b together encode a C-terminally-extended frameshift protein pp1ab. The ORF1a/b locus encodes 16 nonstructural proteins, in which pp1a and pp1ab are first produced and then further processed via auto proteolysis by the viral-encoded polymerase in the virion into nsp1-nsp16 (**Table 2**). The replicase locus encoded nonstructural proteins (nsp1-nsp16) have all functions required for replication and transcription in the virus's life cycle (28).

Two coronavirus proteases (nsp5 and nsp3) play an essential role in converting the pp1a and pp1ab into nsp1-nsp16 (29). Protein nsp5 is the 3-chymotrypsin-like

protease enzyme (3CL^{pro}), the main protease (M^{pro}), which cleaves the nsp4-nsp11 of pp1a and nsp4-nsp16 part of pp1ab, and digests the polyproteins at least in 11 conserved sites, first through the autolytic cleavage of itself from pp1a and pp1ab. Nsp3 is the papain-like protease enzyme (PL^{pro}), and its primary function is to process the viral polyprotein pp1a to release nsp1-nsp3. SARS-CoV-2 protease PL^{pro} preferentially cleaves the ubiquitin-like protein interferon (IFN)-stimulated gene 15 (ISG15), and, upon infection, it contributes to the cleavage of ISG15 from interferon responsive factor 3 (IRF3) and attenuates the IFN response (30).

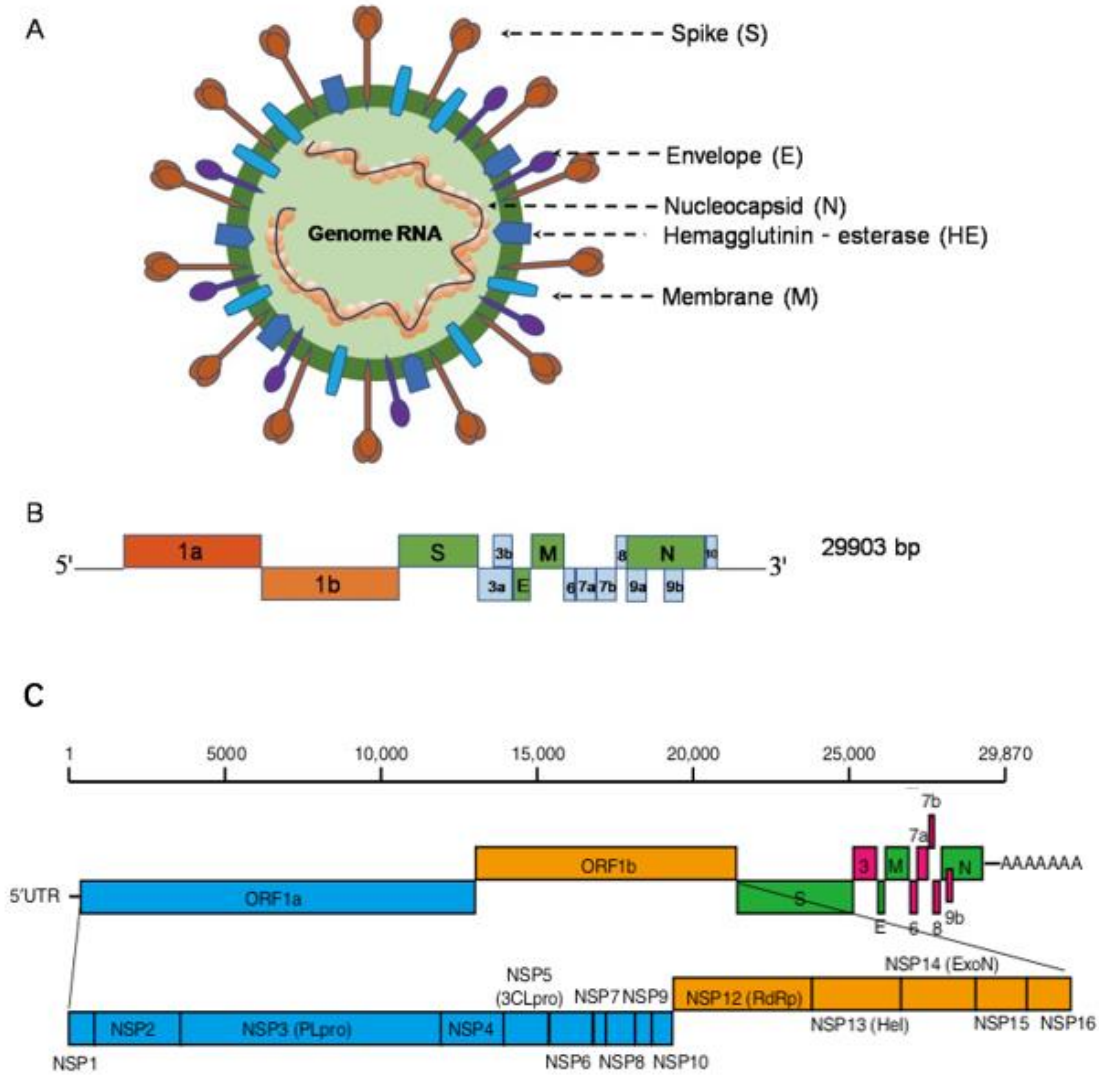

Figure 1. Schematic presentation of SARS-CoV-2 A) Virion Structure, B) RNA genome structure (31), C) Encoded proteins (32)

Nonstructural proteins are also involved in the innate host response, anchoring the viral replication complex, viral replication and transcription, and mRNA processing (28). Viral replication and transcription are mediated by the replication-transcriptase complex (RTC), formed by several nonstructural proteins (nsp7-nsp16), N protein, and multiple host proteins in the infected cell. The RNA dependent RNA polymerase (RdRP, nsp12), helicase (nsp13), nsp7, and nsp8 are central enzymes for RNA processing (28, 29). Nonstructural proteins nsp3, nsp4, and nsp6 are involved in building the double-membrane vesicles required for RNA replication in the cytoplasm. The nonstructural proteins nsp1 and nsp2 are likely to modulate the host cell response through interacting with host cellular factors to promote viral gene expression and

immune-evasion in part by interfering with the IFN-mediated signaling (33).

Computational analysis has indicated that some segments within nsp2 and nsp3 have no homology with other coronaviruses such as SARS and bat SARS-like coronavirus (34). These mutations in nsp2 and nsp3 might provide indications for examining the difference between SARS-CoV-2 and other coronaviruses in infectivity and disease clinical features. The primary function of nsp3 is to process polyproteins to release nsp1-nsp3 (35), indicating its viral replication role. In mice, nsp9 was found to be essential for the replication of SARS-CoV (36) as well as other coronaviruses (37)

Other nonstructural proteins are involved in the antiviral response of the host immune system. In screening 23 proteins of SARS-CoV-2 including 15 nonstructural proteins (nsp1-nsp10, nsp12-nsp16), four structural proteins, and four accessory proteins (ORF3, ORF6, ORF7, ORF8), Lei et al. found that nsp1, nsp3, nsp12-nsp14, ORF3, ORF6, M proteins might inhibit Sendai virus-induced IFN-β promoter activation, but nsp2 and S proteins showed the opposite effect (32).

Structural proteins

The downstream open-reading frames (ORFs) of the RNA genome encode four structural proteins required for assembling a new RNA genome during replication (**Table 3)**. The Spike (S) protein is the largest structural protein encoded by the RNA genome. The receptor-binding domain of the S protein strongly binds to the human ACE2 receptor (38). Therefore, S protein may be a target for inhibition of viral entry and development of antibody-based therapeutics to prevent the disease. The S protein has two functional units, S1 (bulb part) for receptor binding and S2 (stalk part) for membrane fusion; their functions may need other human receptors or proteases such as TMPRSS2 and furin to activate and facilitate the viral entry into host cells. They will be discussed subsequently under Host Cellular Factors.

The envelope (E) protein is a small membrane protein that is anchored on the viral envelope and plays a role in the virion assembly and has additional effects on the infected cells of the host. A SARS-CoV lacking E protein adapted to infect mice *in vivo* seemed to be attenuated and could serve as a promising vaccine candidate (39). The E protein alters coronavirus virulence by regulating the cell stress response and apoptosis during host cell infection (40). In mice, the SARS-CoV E protein PDZ-binding motif was involved with the immunopathology, likely through interacting with syntenin and P38 MARK activation (41).

The membrane (M) protein is a multi-membrane spanning protein and the most abundant in the viral envelope. It provides structural support for the virion and plays a role in the assembly and construction of virion particles. M proteins can have interactions among themself and with other structural proteins.

N protein complexes with the genome RNA to form the virial nucleocapsid within the viral membrane and interact with the M in the assembly. The N protein may play a role in replicating RNA. Antibodies to N and S protein have been considered targets to diagnose infection with coronavirus (42). The N protein, along with other accessory proteins (e.g., ORF6 and ORF8), has been shown to inhibit the type 1 IFN signaling pathway (43).

Accessory proteins

The viral genome of SARS-CoV-2 encodes accessory proteins including ORF3a, ORF3b, ORF6, ORF7a, ORF7b, ORF8, ORF9b, ORF9c, and ORF10 (27, 31, 44-46). They may play a critical role in determining virulence and modulating host immune response to induce pathogenicity caused by the viral pathogen. In the case of SARS-CoV, ORF3a partnering with E protein may play a critical role in maximal replication and virulence, and a coronavirus lacking both proteins is not viable (47). ORF3a activates both NF-kB and the NLRP3 inflammasome (48), promoting the secretion of anti-inflammatory cytokines IL1B and IL18. Mutations in functional domains of ORF3a are linked to virulence, infectivity, and virus release (49). By contrast, ORF3b may not code for a functional protein in all coronaviruses, as immunohistochemical analysis of tissue biopsies of patients with SARS failed to detect its presence *in vivo* (46)

In addition, ORF6, ORF8, and N proteins can inhibit type 1 interferon signaling pathway (43), a key component of the antiviral response of the host innate immune system. ORF6 may play a critical role in inhibiting both IFN-β production and downstream signaling (32). As mentioned above, ORF7a is also on the envelope, and large-deletions have been detected in ORF7a, resulting in in-frame gene fusions (50). SARS-CoV ORF7a interacts with the ribosomal transport proteins and has been shown to inhibit cellular translation and activate p38 MARK (51).

Genomic mutations

The coronavirus consists of an RNA genome that is naturally subject to a rapid genetic mutation. Mutations may change the dynamics of transmissibility and pathogenicity of SARS-CoV-2. Therefore, monitoring possible mutations is important in developing strategies for prevention and medications. With a bioinformatics investigation of the structural genomics and existing database of the related-SARS viruses, Srinivasan et al. provided structural genomics and interactome roadmaps of the SARS-CoV-2 virus (44). In the nonstructural, structural, and accessory proteins encoded by SARS-CoV-2 RNA genome, a large novel insert was found between two putative functional domains in nsp3, and four inserts found in S protein were unique to SARS-CoV-2. Of note, the nsp3 is a papain-like protease (PL^{pro}) that processes the viral polyprotein to release nsp1-nsp3, and it may facilitate the viral evasion of host immune response (52).

Another study focused on detecting mutations within the strains of SARS-CoV-2 to understand the mode of transmission and clinical manifestations. With nearly 5000 complete sequences of the SARS-CoV-2 genome, mostly from the US and European countries, Zhao et al. performed a phylogenetic and structural analysis, aiming to identify the human-adaption-related mutation (53). While noting a lower genetic distance of these genomic sequences, they found 11 residuals with high-frequency substitutions, located at nsp2, nsp5 (3CL-protease), nsp6, nsp12 (RdRP), nsp13 (helicase), ORF3a, ORF8, and structural protein N and S (53). These are essential proteins for viral replication. Furthermore, deletion of amino acids in SARS-COV-2 nps1 protein could affect the regulation of viral replication and the host's gene expression. Nsp1 as leader protein is the most critical determinant of viral replication and the host's antiviral innate immune response, mainly through reducing the host's IFN-α expression. In SARS-CoV, residuals in nsp1 were found to affect the nsp1 inhibition of host gene expressions or antiviral signaling (54). Benedetti et al. found that deletion of three amino acids in SARS-CoV-2 nsp 1 protein could affect the protein's C-terminal structure, which is important for regulating viral replication and the negative effect of host gene expression (55). A mutation was detected in the SARS-CoV-2 nsp6 (56), and mutations in ORF3a are found in six functional domains of SARS-CoV-2, likely linked to virulence and infectivity, ion channel formation, and virus release (49).

Table 2. Proteins encoded by SARS-CoV-2 RNA genome

Genes	Protein	AA	Functions
ORF1ab	nsp1	~100	A potentially major virulence factor in the cytoplasm of infected cells that may interfere with the cellular translational machinery and shut down the host mRNA translation through ribosome-binding (33). SARS-CoV nsp1 promotes viral gene expression and immunoevasion in part by interfering with the virus- and IFN-mediated signaling (54). It might be a potential drug target.
	nsp2	~628	SARS-CoV nsp2 interacts with host factors prohibitin 1 (PHB1) and PHB2, two evolutionarily conserved proteins with cellular functions of cell cycle progression, migration, cellular differentiation, and apoptosis, and mitochondrial biogenesis (57). It is likely involved in altering the host cell environment. Nsp2 and S may have a stimulating effect on IFN induction (32). Nsp2 is involved in the endoplasmic reticulum (ER) Ca(2+)signaling and mitochondrial biogenesis(58).
	nsp3	~1945	A papain-like protease (PL^{pro}), its primary function is to process the viral polyprotein to release nsp1-nsp3. PL^{pro} protease enzyme also has the function of de-ubiquitinating and de-ISGylating (interferon-stimulated gene 15, ISG15) from host cell proteins and aids in viral evasion of the host innate immune response (30, 35); interacting with nsp4 and nsp6.
	nsp4	~500	Is involved in the formation of double-membrane cytoplasmic vesicles (28). Interaction with nsp3 is required for viral replication. Loss of nsp3-nsp4 interaction eliminates viral replication. Nsp4 protein interactors are involved in endoplasmic reticulum (ER) homeostasis (58).
	nsp5	~306	The main protease (M^{pro}, also $3CL^{pro}$) cleaves at least 11 conserved sites in polyproteins pp1a and pp1ab to release nsp4-nsp16. It is necessary for viral replication and its survival in the host cell (59).
	nsp6	~290	Induces double-membrane vesicles in infected cells with nsp3 and nsp4 in SARS-CoV (60), nsp6 also limits autophagosome expansion, induced directly by nsp6 or indirectly by starvation or chemical inhibition of mTOR signaling (61).
	nsp7	~83	Is formed with nsp8 as a co-factor for the RaRP (nsp12) and may have processivity or RNA primase function (29, 62).
	nsp8	~198	Is formed with nsp7 as a co-factor for the RdRP (nsp12) and may have processivity or RNA primase function (62). Mutation of specific residues in nsp8 is lethal to SARS-CoV by impacting RNA synthesis (29).
	nsp9	~113	Is believed to mediate viral replication, overall virulence, and viral genomic RNA reproduction (37).
	nsp10	~139	High sequence similarity with SARS-CoV nsp10 binds to nsp14 and nsp16 to stimulate their respective 3'-5' exoribonuclease and 2'-O-methyltransferase activities building the viral mRNA capping machinery (29, 63).
	nsp11	~13-23	A pp1a cleavage product at the boundary of nsp10 and nsp11, and with function unknown (29).
	nsp12	~932	RdRP forms a complex with nsp7 and nsp8 and performs replication and transcription of the viral genome (29, 64). It has more than 95% identity to the SARS-CoV polymerase, which is inhibited by nucleoside analog Remdesivir. The active site of SARS-CoV-2 RdRP is formed by conserved catalytic motifs A-G, of which A-E are located within the palm subdomain, and F and G are within the finger subdomain (65, 66).
	nsp13	~601	A helicase forming the replicase-transcriptase complex with nsp12 for viral genome replication is involved in viral mRNA capping and associated with nucleoprotein in membranous complexes (67).
	nsp14	~527	It has both 3'-5' exoribonuclease and N7-guanine methyltransferase (viral mRNA capping) activities and interacts with nsp10 (29, 68).
	nsp15	~346	An endoribonuclease necessary for viral replication and its survival in the host cell. Loss of nsp15 affects both viral replication and pathogenesis (69).
	nsp16	~298	It interacts with and is activated by nsp10. Nsp16 and nsp10 form a complex to catalyze the methylation of viral RNA cap (70). Nsp16 may also work against host cell antiviral sensors (29).

ORF2	S	~1273	The Spike full-length protein precursor is cleaved into glycosylated subunits, S1, binding to the host's receptor ACE2, and S2 to mediate viral and host membrane fusion (71).
ORF3a	ORF3a	~275	A transmembrane protein that forms a viroporin 3a in SARS-CoV can modify the host's cell membrane to facilitate viral release from infected cells. Full-length protein E and 3a are required for maximal replication and virulence, and a virus lacking both proteins is not viable (47). ORF3a interacts with accessory protein 7a, M, S, and E. ORF3a also activates both NF-kB and the NLRP3 inflammasome (72), contributing to the generation of the cytokine storm. It induces apoptosis in the host cell (73).
ORF3b	ORF3b	~22	Along with N and ORF6, ORF3b appears to block induction of IFN-I, and the variant is present in other related viral genomes in bats and pangolins (74).
ORF4	E	~75	A small membrane protein involved in viral assembly, budding, envelope formation, and pathogenesis. It is viroporin and forms a homopentameric ion channel; it interacts with M, N, 3a, and 7 (75).
ORF5	M	~222	A multi-membrane spanning protein on the viral envelope and the most abundant structural component is conserved and highly similar to its SARS-CoV counterpart. It interacts with N for virion RNA packaging and with accessory proteins 3a and 7a. It may aid in proliferation, replication, and immune evasion (76).
ORF6	ORF6	~61	It might be associated with the virulence of SARS-CoV as an antagonist of type I IFNs, and it is involved in the viral escape from the host's innate immune system (32).
ORF7a	ORF7a	~121	A type I membrane protein interacts with bone marrow stromal antigen 2 (BST-2) in SARS-CoV. BST-2 binds virions to the host's plasma membrane. ORF7a binding inhibits BST-2 glycosylation and interferes with this restriction activity. It interacts with S, M, E, and ORF3a in SARS-CoV (77).
RF7b	ORF7b	~43	It appears to be a viral attenuation factor for SARS-CoV and may influence the human infectivity of SARS-CoV-2(78).
ORF8	ORF8	~121	It might be a luminal ER membrane-associated protein that may trigger ATF6 activation and affect the unfolded protein response (UPR). It may be involved in the human infectivity of SARS-CoV-2 (79).
ORF9a	N	~419	Binds viral genomic RNA and forms a helical ribonucleocapsid, is involved in genome protection, viral RNA replication, virion assembly, and immune evasion (including IFN-I suppression), and interacts with M and nsp3 proteins (80).
ORF9b	ORF9b	~97	Overlaps with N gene in some strains of SARS-CoV-2 isolated in the US (46). In SARS-CoV, the encoded protein localizes to mitochondria. It affects mitochondrial morphology and function and suppresses the innate immunity of host cell IFN response by targeting mitochondria and the MAVS/TRAF3/TRAF6 signaling (81).
ORF9c	ORF9c	~70	Overlaps with N gene in some strains of SARS-CoV-2 isolated in the US (46). The encoded protein is associated with membrane-associated proteins in multiple organelles, including ER, Golgi, mitochondria, and surface membrane, which suppress antiviral response in the cell through downregulating IFN signaling and antigen processing (82).
ORF10	ORF10	~38	ORF10 is unique to SARS-CoV-2 among HCoV and encodes a peptide of only 38 amino acids (46), which interacts with factors in the CUL2 RING E3 ligase complex and thus may modulate ubiquitination (68).

Sources: https://www.genetex.com/MarketingMaterial/Index/SARS-CoV-2_Genome_and_Proteome;
Nsp, nonstructural proteins encoded by ORF1a and ORF1b gene; S, Spike glycoprotein encoded by ORF2; E, envelope protein encoded by ORF4; M, membrane protein encoded by ORF5; nucleocapsid protein encoded by ORF9a; the RNA-dependent RNA polymerase (RdRP)

VIRAL REPLICATION

Attachment and cell entry

The viral attachment and host cell entry is the first step of viral replication in which the S glycoprotein binds the receptors (e.g., ACE2) on the surface of host cells (71). The subunit S1 binding specific receptor causes a drastic conformational change in the subunit S2 and then leads to a fusion between the virus envelope and the host cell's cellular membrane. Many proteases, including the host protease, TMPRSS2, can accomplish a cleavage of S2 protein to facilitate the viral fusion with the host cell membrane (71, 83). Also, SARS-CoV-2 S glycoprotein harbors a cleavage site at the boundary between S1 and S2 units (84, 85), activated by furin, a serine endoprotease, for facilitating the fusion of cell membrane. TMPRSS2 and furin are essential for proteolytic activation of the SARS-CoV-2 S protein in human airway cells (86).

The furin cleavage site in the S protein is not found in SARS-CoV (85), which, together with the receptor-binding domain (RBD) of the S protein, might contribute to the high infectivity of SARS-CoV-2. The furin cleavage site is polybasic, allowing an effective cleavage by furin and other proteases, and polybasic furin cleavage sites are often found in hemagglutinin proteins in avian and influenza viruses (87). Also, an inserted proline and other insertion, PRRA, at this site are predicted to add O-linked glycans to three variants, which flank the polybasic cleavage site (88).This addition of O-linked glycans may enable S protein bind additional receptors as described below. In addition, the S protein RBD of SARS-CoV-2 that has an optimal binding affinity to ACE2 is structurally different from that of SARS-CoV (88). The SARS-CoV-2 binding

affinity to ACE2 is more than 10-fold higher than SARS-CoV (89, 90). Therefore, the feature of the furin cleavage site and different RBD sequences likely constitute an effective viral attachment and entry, leading a rapid transmission.

The virus can also enter the host cell through direct endocytosis and then, through a cathepsin-mediated process, release the viral RNA genome into plasma (91). Other host proteins (e.g., CD147, GRP78) and host proteases (e.g., cathepsin L/B, trypsin) might be involved with the viral entry of SARS-CoV-2 into the host cell (91), which may establish an infection and affect the infectivity and clinical outcomes.

Translation and RNA replication

The RNA genome's translation and replication start after the virus disassembles within the host cells and releases its nucleocapsid and viral RNA into the host cell cytosol. The nucleocapsid undergoes an uncoating process to release the genomic RNA. The host ribosomes then translate the viral RNA to produce nonstructural proteins. This translation process starts with the replicase locus where the ORF1a and 1b are first translated to produce replicase polyproteins pp1a and pp1ab, which are further processed through proteolysis by viral-encoded proteases into nonstructural proteins (nsp1-nsp16). Some nonstructural proteins involved in forming the replicase-transcriptase complex (RTC) include the RNA-dependent RNA polymerase (RdRP, also known as nsp12), which uses nsp7 and nsp8 as auxiliary factors and nsp13, the helicase. RdRP, as a critical component, catalyzes the synthesis of viral RNA and plays a central role in the viral replication of SARS-CoV-2 (66). The nsp13 replicase is a critical component for viral replication and has the highest sequence conservation across the CoV family (92).

RdRP transcribes the full-length positive strand of viral genomic RNA to synthesize negative-strand genomic and subgenomic RNA template for positive-strand new genomic RNA and subgenomic RNA transcripts. The most abundant transcripts are N, S, 7a, 3a, 8, M, E, and 7b (27). The subgenomic transcripts are translated to produce structural (S, E, M, N) and accessory proteins and genomic RNA to form the viral particle.

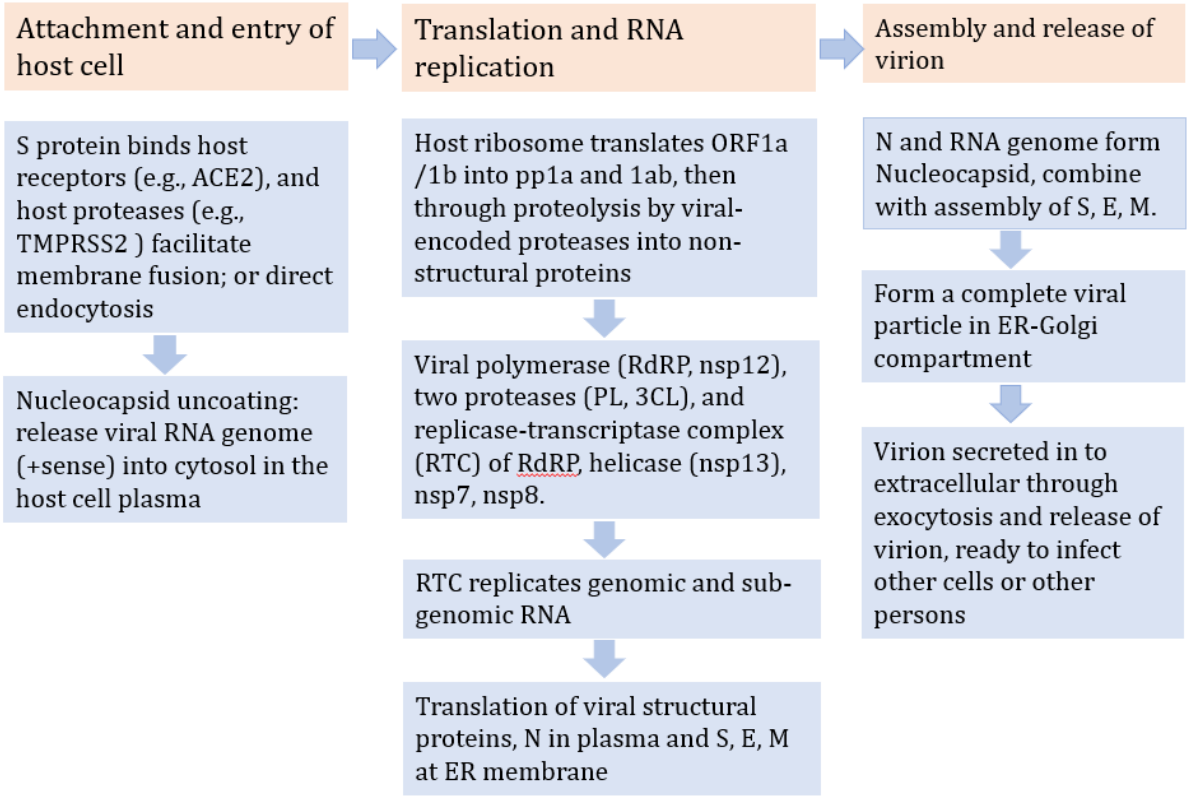

Figure 2. Viral replication process of SARS-CoV-2

Assembly and release of virion

The S, E, and M proteins enter the endoplasmic reticulum (ER), and the N protein combines with the new positive-strand genomic RNA to form a nucleocapsid complex. They merge into a complete viral particle in the ER-Golgi apparatus compartment and are secreted into extracellular through exocytosis. The new virions are then released outside the host cell.

HOST CELLULAR FACTORS

Coronaviruses can infect a variety of species, some of which may impact human life. Besides the ongoing SARS-CoV-2 pandemic that has an unprecedented impact on human history, coronaviruses can infect major domestic animals such as pigs, cattle, and chickens, significantly impacting economic activities and daily human life. More importantly, because they process an RNA genome, coronaviruses are subject to high recombination and, therefore, more likely to have a host switching. For example, the three HCoVs that can cause severe diseases to humans (SARS, MERS, and COVID-19) have migrated from a natural host such as a bat to a domestic host before infecting humans and causing diseases. The recurrent pandemic of COVID-19 indicates the ability of CoVs to have host switching and cause human-to-human transmission.

Host cellular factors involved in the infection cycle of HCoVs are essential for understanding the viral infectivity and transmission and developing effective preventive and therapeutic strategies. Several host factors are involved with coronavirus infection (**Table 2**), mainly HCoVs, through that host factors associated with the attachment and entry of host cells. In addition, a genome-wide screen of small interfering RNA (siRNA) reveals that vasolin-containing protein (VCP) plays a role in the early stage of infection with IBV, an avian infectious bronchitis virus in human cells (93).

With the technological advances in large-scale molecular biology and computational and bioinformatics tools, additional host factors have been rapidly indicated to affect the entry of viral SARS-CoV-2 into the human host cells (**Table 3)**. Besides the main receptor ACE2 and transmembrane protease, serine 2 (TMPRSS2) are known to be involved with infections of other HCoVs, additional receptors and proteases, or even different virus routes by which SARS-CoV-2 entering host cells are discovered (94).

Table 3. Host cellular factors involved in viral attachment and entry of coronaviruses

Host factor	Description	Virus name abbreviation	Role for viral protein
APN (22)	Human or porcine aminopeptidase N	229E, [TGEV]	Cell surface receptor
CTSL (95)	Cathepsin L	SARS, SARS-CoV-2	Mediates cleavage of the S1
CTSB (71)	Cathepsin B	SARS-CoV-2	Cleave S protein in the cell
CD147 (96)	Basigin (BSG)	SARS-CoV-2	A receptor on the host cell
ACE2 (97)	Angiotensin-converting enzyme 2	SARS-CoV, CoV-2, NL63	Receptor
DDP4 (98)	Dipeptidyl peptidase-4, CD26	MERS, 229E	Receptor
9-O-ac-sia (99)	9-O-acetylated sialic acid	OC43, HKU1	Receptor
Furin (100)	Preprotein convertase subtilisin/kexin 3, PCSK3	SARS-CoV-2, MERS, [IBV]	Cleave and activate S protein
GRP78 (101)	Binding immunoglobin protein	SARS-CoV-2, MERS	Receptor binding
LY6E (102)	Lymphocyte antigen 6E	All HCoVs	Restrict viral entry
Sialic acid (103)	In the brain and neuronal transmission	SARS-CoV-2, MERS	Receptor
TMPRSS11D (104)	Transmembrane serine protease 11D	SARS-CoV-2, SARS, 229E	Cleave and activate S protein
TMPRSS2 (71)	Transmembrane serine protease 2D	SARS-CoV-2	Cleave and activate S protein
VCP (93)	Valosin-contacting protein	229E, [IBV]	Cleave and activate S protein

Host factors associated with susceptibility to COVID-19 are divided into three sequential stages. They include 1) host cell exposure to the pathogen, 2) host cellular factors (host receptors and proteases) that modulate pathogen entering into the host cell, and 3) host response that is determined by individual-specific immunity and immune system response. Unlike the other six HCoVs that can cause human infections, SARS-COV-2 can be affected by more host receptors or cellular factors that can establish an attachment and/or facilitate viral entry into the host cell. Identifying new receptors and host cellular factors might help prevent SARS-CoV-2 infections after exposure by altering their expression (105).

ACE2

Angiotensin-converting enzyme 2 (ACE2) is a zinc-containing metalloenzyme located on the surface of endothelial and other cells (106) and moderate to highly expressed in the human upper respiratory tract, small intestine, colon and rectum, gallbladder, kidney, pancreas, testis, and fallopiantube (107). It serves as a receptor for SARS-CoV-2 and SARS-CoV (108, 109) and NL63 (95). The SARS-CoV-2 S protein receptor-binding domain (RBD) and ACE2 have a compact conformation, which indicates an increased binding affinity (97, 110). The SARS-CoV-2 virus has been isolated in the human airway epithelial cells in patients with COVID-19. The *ACE2* gene is highly expressed in the oral mucosa's epithelial cells (111), other human tissues such as the gastrointestinal tract, liver and gallbladder, kidney, urine, and male bladder tissues, and heart muscle. ACE2 has genetic heterogeneity (112), which may lead to a variation in infectivity among different populations.

Animal studies show that a high dose of an ACE inhibitor (ACEi) or angiotensin receptor blockers (ARB) may increase the level of ACE2 (113). It is speculated that continuing use of ACE inhibitors or ARBs, two common antihypertensive drugs during the pandemics, may elevate ACE2 which might increase the risk of SARS-CoV-2 infection and viral load and lung injury in humans (114). So far, however, several observational studies have not

provided any supporting evidence. A large prospective study of more than 8 million adult participants showed that using ACEi might reduce the risk of COVID-19 but did not significantly increase the risk for admissions to an intensive care unit (ICU) (115). Another case-population study in Spain showed that the use of ACEi did not increase severe COVID-19 but reduced the likelihood of required hospital admission in patients with diabetes (116). However, black Africans who used ACEi were observed with an increased risk of COVID-19. In fact, other studies in animals showed that SARS-CoV induced acute lung injury could be attenuated by blocking the renin-angiotensin pathway (117).

The role of ACE2 in developing COVID-19 has not been determined and needs to be further studied. ACE2 is a receptor bound by the S protein of three HCoVs, SARS-CoV-2, SARS-CoV, and HCoV-NL63 that cause diseases to humans. However, their infectivity, disease severity, and transmission mode of SARS-CoV-2 are markedly different, indicating that the ACE2 receptor is necessary for establishing an infection but not sufficient to account for all the features of SARS-CoV-2 infection. In addition, a protein expression study of various human cells and tissues indicates that ACE2 expression is limited in lungs, with no or low expression in a subset of cells (118). The infection might be established in the upper respiratory tract where ACE2 protein has a medium level of expression in the nasopharynx and bronchus, according to the human protein atlas (107). There might be additional features of SARS-CoV-2 or pathogen-host interactions that influence its differences from SARS-CoV and HCoV-NL63 infection. Current clinical observations show that severe COVID-19 is associated with underlying health conditions and advanced age.

ACE/ACE2 is important for maintaining physiological hemostasis and has implications for chronic health conditions (119, 120). The functions of ACE and ACE2 counter each other in the classical renin-angiotensin system (RAS). ACE, moderately expressed in lung, kidney, gastrointestinal tract, and reproductive tissues (107), is a central component of the RAS that controls blood pressure by regulating the body's volume of fluids. It converts the inactive pro-hormone angiotensin I (Ang I, angiotensin 1-10), a decapeptide, by removing two C-terminal residues into the active vasoconstrictor angiotensin II (Ang II, angiotensin 1-8). Ang II is a highly active octapeptide that, through binding angiotensin type 1 receptor (AT1R), causes vasoconstriction and other proinflammatory activities, which may cause cell injuries (**Figure 1**). Therefore, ACEi and ARBs aim to interfere with Ang II/AT1R pathway to reduce blood pressure and protect cells from damage.

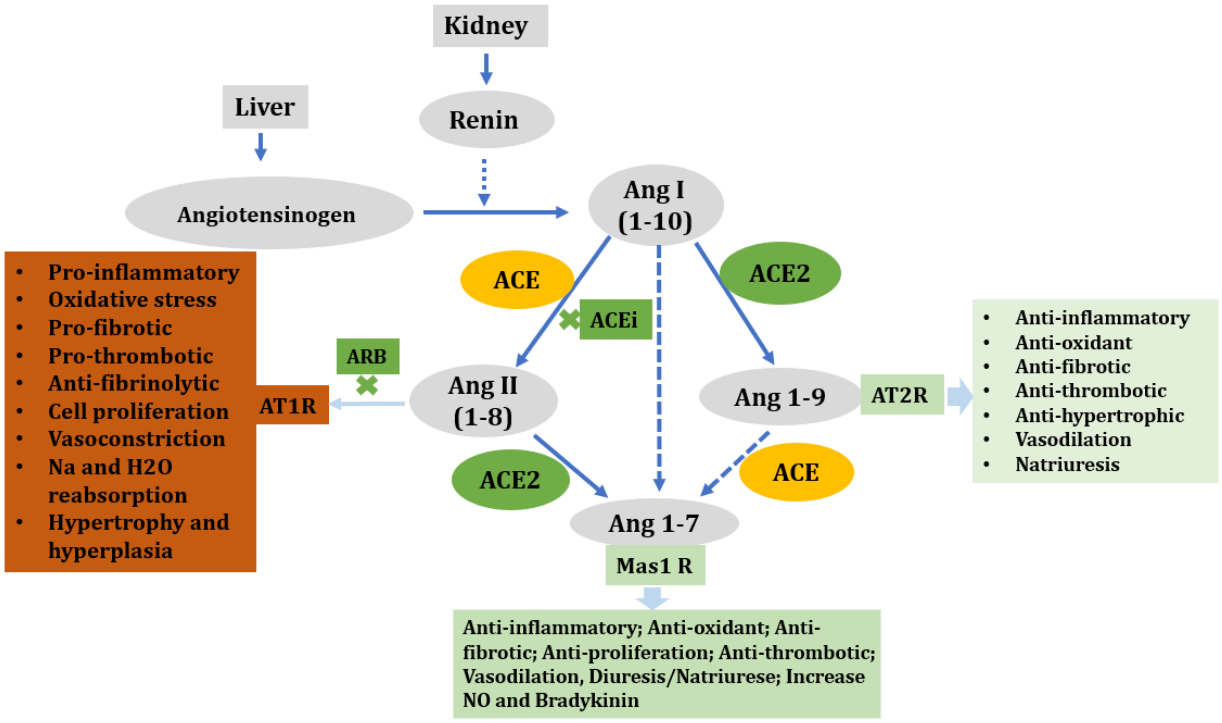

Figure 3. The Role of ACE/ACE2 in the Renin-angiotensin System (RAS)

On the other hand, the endogenous ACE2 counter the effects induced by ACE in the classical RAS (121). ACE2 is discovered as a first homolog gene of ACE and exhibits more than 60% similarity of ACE sequence. ACE2 converts

Ang II to a vasodilator Ang 1-7, a heptapeptide, which, through binding the Mas 1 oncogene product receptor (Mas1 R), stimulates the nitric oxide synthase (NOS) to produce a counter-regulatory response to Ang II-mediated effects. Therefore, Ang 1-7/Mas 1R causes vasodilation and anti-inflammatory activities that may exhibit a cell protective effect (Figure 1). In addition, ACE2 has been shown to metabolize Ang I to Ang 1-9, a biologically active peptide that may act through angiotensin type 2 receptor (AT2R). Ang 1-9/AT2R may serve as an antagonist of the classical RAS signaling to produce cell protection (122).

An imbalance of ACE and ACE2 indicates a disturbance in the RAS system. The Ang II/AT1R pathway can activate immune cells and trigger the proliferation of splenic lymphocytes (123), inducing inflammation, which has been indicated in the pathological effect of RAS dysfunction in cardiovascular disease. Recently, ACE/ACE2 imbalance has been considered to play a key role in the inflammatory processes in cardiovascular, cardiac hypertrophy, pulmonary hypertension, lung injury, sepsis, and acute pancreatitis (120). Since SARS-CoV-2 utilizes ACE2 receptors to enter the host cells, it may deplete ACE2 receptors and cause an increase in ACE/ACE2 ratio and RAS dysfunction, leading to a worsening outcome in individuals infected with SARS-CoV-2 (124). In a report of 23,188 patients with COVID-19, 69% of patients were found with hypertension, suggesting that the RAS system's imbalance may increase the susceptibility to SARS-CoV-2.

ACE2 depletion might be associated with the severity of COVID-19. In a mouse model of acute lung injury, ACE2 deletion causes more severe diseases, suggesting a protective role for ACE2 in lung tissues (117). When SARS-CoV-2 S protein binds to ACE2, the depletion may reduce availability for its normal protective functions. Therefore, it, in turn, may result in acute respiratory failure and other organ-associated damage (117), commonly observed in severe COVID-19 (125). Depletion of ACE2 may thus play a causative role in the lung injury caused by SARS-CoV and SARS-CoV-2, as plasma Ang II is elevated in patients with critical COVID-19 compared to mild cases (126). A high ratio of ACE to ACE2 may cause harm to the lungs and other organs due to the dysfunction of RAS. Also, ACE and ACE2 might have a role in the Kallikrein-Kinin system (KKS). This humoral pathway modulates the blood coagulation system and endothelial cell growth and angiogenesis; all are related to the common pathogenesis of severe COVID-19 (127).

Of note, MERS-CoV also causes a similar lung disease without targeting ACE2 as a receptor, so other viral molecules and host factors must be involved in causing the severe lung diseases associated with SARS-CoV-2 infections. The effects of SARS-CoV-2 on the respiratory system and other major functioning organ systems in the human body are borne out by multi-organ histopathological manifestations (128-131).

TMPRSS2

TMPRSS2 is an enzyme belonging to the serine protease family and cleaves the S2 subunit of SARS-CoV-2 S protein to facilitate viral fusion with the host cell membrane (71, 84, 85). Not only the SARS-CoV-2 virus, but other viruses such as SARS-CoV, the influenza virus H1N1 also depend on the TMPRSS2 activation for virus entering the host cell (132). An animal model shows that TMPRSS2 contributes to virus spread and immunopathology in the airways after infection with SARS-CoV-2 (133).

The involvement of TMPRSS2 might support some observations on the sex bias in COVID-19 (134). The *TMPRSS2* was initially identified in prostate cancer and is upregulated in prostate cancer cell lines in response to androgens (135). It also participates in TMPRSS2-ERG gene fusion, the most common gene fusion events in solid tumors, presenting 50% of prostate cancer in European ancestry. Since TMPRSS2 is critical for SARS-CoV-2 viral infection and is upregulated by androgen, a sex bias in the severity of COVID-19 should be investigated with this gene. TMPRSS2 has been proposed as a potential biomarker for the study of COVID-19 (136).

TMPRSS2 inhibitors are available (135) and have been suggested for use in possibly preventing SARS-CoV-2 infection. Primary nasal epithelial cells from human COVID-19 patients treated with azithromycin exhibited TMPRSS11D and TMPRSS2 as top gene downregulation compared with controls, although these were based on a few samples (137).

FURIN

Furin is a protease enzyme encoded by a gene located in oncogene FES's upstream region (FURIN). It is a subtilisin proprotein peptidase that cleaves and processes latent precursor proteins into their biologically active products. The Spike glycoprotein of SARS-CoV-2 is found to harbor a polybasic cleavage site at S1/S2 subunits required for its efficient cleavage by furin, which is essential for S protein-mediated cell-cell fusion and viral entry into human lung cells (138). However, the cleavage site is lacking in other SARS-like coronaviruses (100). Increased cell-cell fusion by this cleavage site at optimized conditions might contribute to the rapid transmission mode of SARS-CoV-2 that is more competent than other SARS-like viruses.

Current evidence indicates that the SARS-CoV-2 enters the host cell by its S protein binding to ACE2 receptor through its cleavage at site S1/S2, first by furin and then at site S2' by TMPRSS2; both are essential for the proteolytic activation of the virus (86). In a study that examined the three gene expression, the co-expression of *FURIN* with *TMPRSS2* was more significant than with *ACE2* in the primary lung cells (139). The antiviral activity of various TMPRSS2 inhibitors combined with a furin inhibitor is more efficient than any single inhibitor alone in human airway epithelial cells (86). In addition, furin might be involved in the pathogenesis of SARS-CoV-2, as it is expressed by T cells, which are essential for maintaining the peripheral immune tolerance and regulating the cell-

mediated immunity (140). Pharmacological inhibition of furin in humans might slow the viral entry into host cells and reduce the infection by SARS-CoV2.

DPP4

Dipeptidyl peptidase 4 (DPP4) is an aminopeptidase protein expressed on the surface of several cell types and is involved with signal transduction, immune regulation, and apoptosis. It is a serine protease known to cleave substrates such as growth hormones, chemokines, neuropeptides, and vasoactive peptides and inactivate them after cleavage (141, 142). Aminopeptidase N (APN) is a receptor for HCoV-229E and TGEV (143, 144). DPP4 is an abundant and ubiquitous protein that plays functional roles in metabolism, the immune and endocrine responses, bone marrow mobilization, cancer growth, and cell adhesion (145). More specifically, its activity regulates glucose homeostasis and inflammation. DPP4 has been identified as a functional cellular receptor for MERS-CoV (98). Recently, a molecular docking analysis has suggested that many residuals on DPP4 interact with S1 domain of SARS-CoV-2 (146). Coronavirus enters and hijacks the host cells primarily through the S1 domain of the S protein interacting with host proteins such as DPP4, which cleaves the amino-terminal dipeptide to activate T-cell, a key immunoregulatory factor in viral infection (146, 147).

DPP4 might explain the severe COVID-19 response that is downstream of virion binding to the ACE2 receptor. Plasma DPP4 is higher in individuals with obesity, metabolic syndrome, and type 2 diabetes, and older adults, conditions that are associated with the severity and unfavorable outcomes of COVID-19 (145, 148). In human tissues, DPP4 is strongly expressed on the surface of epithelial cells in the liver, kidney, gut, lungs, pancreases, and is present on capillary endothelial cells (145). These are consistent with the multi-organ pathophysiology of severe COVID-19 and MERS; also, ACE2 is minimally or not expressed in the lung tissues and is not a receptor for MERS-CoV. Because DPP4 inhibitors have been approved for treating patients with type 2 diabetes, they might help prevent SARS-CoV-2 infection and disease progression (149).

CD147

CD147 has been demonstrated to be a novel receptor for SARS-CoV-2 S protein (150). It is an extracellular matrix metalloproteinase inducer (EMMPRIN) encoded by gene basigin (BSG) and a transmembrane glycoprotein of the immunoglobin superfamily. CD147 also acts as a receptor for *plasmodium falciparum*, a pathogen that causes malaria by invading red blood cells (151). Drugs interfering with S/CD147 binding may inhibit the pathogen invasions and protect other cells, including progenitor/stem cells. Humanized anti-CD147 antibodies can block host cell invasion entirely by the human malaria parasite, significantly by SARS-CoV-2 *in vitro* (152) and human patients with COVID-19 (153). Patients treated with anti-CD147 antibodies have significantly reduced time to viral testing negative (median, three vs. 13 days) and improved clinical outcomes, compared with other hospitalized patients (153). In addition, SARS-CoV N protein may bind to HAb18G/CD147 to invade the host cell (154).

CD147 acts as the principal upstream stimulator of matrix metalloproteinases (MMPs), closely related to MMPs. Their expression is often increased in inflammation and on the surface of tumor cells. MMP1 and MMP7 are potential peripheral blood biomarkers for idiopathic pulmonary fibrosis (155), which is observed in severe COVID-19 (156). Anti-CD147 antibodies can inhibit the TGF-β induced proliferation and the differentiation of fibroblasts into myofibroblasts, which are originated from resident fibroblasts, pericytes, and resident stem cells (152). Thus, anti-CD147 antibodies could also be used to prevent pulmonary fibrosis in the early stage of COVID-19.

In a gene expression study of SARS-CoV-2 related molecules, *ACE2* and *TMPRSS2* were co-expressed in the epithelial cells of lung and skin, while *CD147* and *CD26* (DPP4) were expressed in both epithelial and immune cells (157), which might imply alternative routes of infection for severe COVID-19.

GRP78

The glucose-regulated protein 78 (GRP78), a binding immunoglobin protein (BiP) encoded by *HSPA5*, is likely a receptor for SARS-CoV-2. GRP78 is a master chaperone protein widely expressed in human tissues and synthesized markedly under cell stress conditions that lead to an accumulation of unfolding polypeptides in the endoplasmic reticulum (ER). It has been shown to play a role in infections with several viruses, including MERS-CoV, Zika, Ebola, and Dengue, and cancer aggressiveness (158). Molecular docking analysis predicts that four Spike protein regions can bind to the substrate-binding domains of GRP78 in recognition of the host cell receptor (101). mRNA expression of *GRP78* in the blood of patients with SARS-CoV-2 pneumonia was found multi-fold higher than other pneumonia patients (159). Further molecular docking analysis found that withaferin A, artemisinin, curcumin, and andrographolide had optimal interaction (e.g., low binding energies) with the GRP78 receptors (160). These four natural compounds have been demonstrated with the efficacy of immunomodulation, anti-inflammation, and anti-anagenesis.

Cathepsins

Cathepsins are a group of endosomal and lysosomal proteases that exhibit endo- and exopeptidase activities. SARS-CoV-2 may enter the host cells through endocytosis depending on low-PH environments, in which phosphatidylinositol-3 phosphate-5-kinase (PIKfyve) and cathepsin L (CTSL) is critical for endocytosis (161). Molecules related to endocytosis might affect the virus entering via this route. A genome-wide loss of function

screening identified top host factors that may reduce the SARS-CoV-2 entry in human alveolar epithelial cells. These top factors are located at endosomal entry (e.g., ACE2, RAB7A), spike cleavage and membrane fusion (CTSL), and endosome recycling (e.g., VSP35), and they can be grouped into different pathways, including the vacuolar APTase proton pump, retromer, and commander complex (162).

Ly6E

Ly6E is a protein belonging to the lymphocyte antigen 6 (Ly6) family and is encoded in humans by the *LY6E* gene. Its primary function is immune regulation, including T-cell activation, proliferation, and development. Ly6E (163) and other IFN-induced cellular proteins such as IFITMs, GILT, ADAP2, 25CH are found to enhance or inhibit the entry of various viruses, including coronaviruses, through viral and host interaction (164-168). Recently, Ly6E was found to inhibit the entry of all HCoVs, including SARS-CoV-2, but through a distinct mechanism from IFITMs (102). LY6E also might mediate the transport of adeno-associated virus across the human blood-brain barrier (169).

Ly6E also plays a role in oncogenesis. Four lymphocyte antigen 6 family members (Ly6D, Ly6E, Ly6H, and Ly6K) were observed to have increased mRNA expression in tumor tissues of bladder, brain and CNS, breast, esophageal, gastric, pancreatic, colorectal, kidney, lung, melanoma, prostate cancer compared with normal tissues (170); over-expression of Ly6E was associated with poor prognostic outcomes of lung cancer, gastric, and breast cancer.

L-SIGN and DC-SIGN

A recent preprint manuscript posted on November 5, 2020 reported a lung cDNA screening. It indicated that the N-terminal domain of SARS-CoV-2 S protein mediates the viral infection through membrane fusion by associating with L-SIGN-a liver/lymph-node specific intracellular adhesion molecule(ICAM)-3-grabbing integrin, and DC-SIGN-a dendritic cell-specific ICAM-3-grabbing non-integrin (94). L-SIGN is a liver-specific receptor for hepatitis virus C (HCV), and both L-SIGN and DC-SIGN plays a role in HCV infection and immunity (171).

Sialic acid

Sialic acid is a monosaccharide widely expressed on the surface of vertebrate cells. N-Acetylneuraminic acid (Neu5Ac) is the predominant sialic acid found in human cells and many animal cells. It has been implicated in host cell entry of various viruses, including adenovirus serotype 37 and enterovirus serotype 70 (172), and MERS-CoV (173). Two HCoVs (OC43 and HKU1) in the same group as SARS-CoV-2 use the 9-O-acetylated-sialic acid as a receptor for viral entry (99).

Recently in silico studies indicate that the S protein of SARS-CoV-2 also binds to sialic acid linked to host cell surface gangliosides as a cellular receptor for viral entry (103, 174), and hydroxychloroquine was found to block SARS-CoV-2 binding to gangliosides (174). It is speculated that binding to the sialic receptor could contribute to the "cytokine storm" that frequently occurs in severe COVID-19 and MERS (175). In addition, sialic acid is a fundamental component of the salivary mucin that protects the glycoproteins. SARS-CoV-2 infection through binding this receptor may reduce sialic acid availability in salivary mucin, causing an increase in gustatory threshold and then gustatory problems. Patients with mild COVID-19 are demonstrated to be prevalent of both anosmia and dysgeusia at a similar rate (134), suggesting that SARS-CoV-2 might use a dual receptor-based strategy for viral entry (103). Furthermore, the sialic acid receptor might be involved in gastrointestinal SARS-CoV-2 infection, which may add fecal-oral route of infection (176).

Plasmin and other proteases

Other proteases are likely to promote viral invasion to host cells and are associated with cytokine storm, ARDS, and multiorgan injuries (177-179). Plasmin has been discussed as a protease of SARS-CoV-2 S protein to facilitate the binding to ACE2 receptor and viral entry and membrane fusion (178). Elevated plasmin may associate with excessive D-dimer in ARDS and chronic conditions such as hypertension and diabetes, often in severe COVID-19 (178). Patients with COVID-19-induced ARDS showed a significantly higher level of fibrin/fibrinogen degradation product and D-dimer relative to non-COVID-19- induced ARDS (180), and D-Dimer level was strongly associated with the fatality of COVID-19 (181). Therefore, high plasmin levels are likely to play an important role in determining disease severity. As such, related inhibitors should have more therapeutic implications for severe patients (182, 183). Of note, plasmin is a co-activator of NF-kB signaling and plasminogen mediate efferocytosis for the inflammation resolution (184), there might be a complex molecular network involved with plasmin in response to the viral pathogen and its sequelae.

In summary, while the genomic structure in SARS-CoV-2 is highly similar to SARS-CoV, the difference in S protein variants might determine that more host cellular factors are involved in viral entry (**Table 4)**; in addition, a distinct roue of endocytosis is indicated. These S protein differences may affect the kinetics of infection and clinical manifestations, and therefore the potential therapeutic approaches. Nonstructural proteins play some essential roles in viral replication, and their interaction with host intracellular molecules may affect the pathogenesis of COVID-19 and lead to variation in clinical manifestations. Therefore, it is critical to conduct timely formal clinical and molecular studies in human patients to understand how viral and host cellular factors influence the viral infection and disease progression. Genome-wide screening for host

factors in patients with COVID-19 would be a promising approach to define molecular-susceptible individuals and develop preventive therapeutics for early treatment for the population at risk exposure.

In addition, an in-vitro screening study of human cell lines may help identify additional cellular factors at a different stage of the viral replication cycle that could indicate therapeutics targets. Given that COVID-19 generally has an incubation period of 4-14 days, it would be valuable to provide preventive therapeutics to those exposed to the infection sources who may have a high likelihood of developing the disease. Hopefully, with newly approved or existing drugs that target the critical molecules of receptors and proteases, the quarantine burden could be reduced before effective vaccines are widely available for vaccination.

Table 4. Host cellular factors for SARS-CoV-2 with other HCoVs

	Beta-CoV					Alpha-CoV	
	SARS-CoV-2	SARS	MERS	OC43	HKU1	299E	NL63
ACE2	++	++					++
CD147	++						
CSTB	++						
CSTL	++	++					
DC-SIGN	++						
DPP4	++		++			++	
Furin	**		**				
GRP78	++		++				
L-SIGN	++						
Ly6E	++	++	++	++	++	++	++
Plasmin	**						
Sialic acid	++		++				
TMPRSS11D	**	**					
TMPRSS2	**						

++ Receptor, **, proteases

CONFLICT OF INTERESTS

The authors have no conflict of interests regarding the publication of this article.

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